Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype

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ABSTRACT

Objective *To define the prevalence of major cardiac defects according to nuchal translucency (NT) thickness at the 11 to 13 + 6-week scan in fetuses with normal karyotype.*

Methods *Specialist fetal echocardiography was carried in 6921 fetuses with normal or presumed normal karyotype at a median gestation of 20 (range 12–35) weeks. The indications for fetal echocardiography were increased NT thickness (n = 3444), detailed second-trimester scan either for assessment of risk of chromosomal abnormalities (n = 2980) or previous or family history of fetal defects (n = 497). The cardiac defects were grouped into six functional categories: septal defect, left inflow obstruction, right inflow obstruction, left outflow obstruction, right outflow obstruction and other.*

Results *Major cardiac defects were identified in 132 (19.1 per 1000) fetuses and the prevalence increased with fetal NT thickness from 4.9 per 1000 in those with NT below the median, to 8.7 for NT between the median and less than the 95th centile, 18.2 for NT between the 95th and 99th centiles, and exponentially thereafter to 35.2, 64.4 and 126.7 for respective NTs of 3.5–4.4 mm, 4.5–5.4 mm and ≥ 5.5 mm. There was no obvious difference in the distribution of NT in the different types of cardiac defects.*

Conclusions *The prevalence of major cardiac defects increases exponentially with fetal NT thickness and in fetuses with NT of 3.5 mm or more it is higher than in pregnancies with a family history of cardiac defects. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Measurement of fetal nuchal translucency (NT) thickness at 11 to 13 + 6 weeks provides an effective method of screening for chromosomal defects[1–3]. Increased NT is also well known to be associated with major cardiac defects and a wide range of fetal malformations and genetic syndromes[4,5]. A meta-analysis of studies examining the screening performance of NT thickness for the detection of cardiac defects in fetuses with normal karyotype, reported that the detection rates were about 37% and 31% for the respective NT cut-offs of the 95th and 99th centiles[6]. This compares favorably with the 10% detection rate achieved by confining specialist fetal echocardiography to pregnancies with a maternal history of diabetes mellitus or exposure to teratogens and family history of cardiac defects[7].

Abnormalities of the heart and great arteries are the most common congenital defects, and they account for about 20% of all stillbirths and 30% of neonatal deaths due to congenital defects[8]. The extent to which fetal NT becomes widely adopted as a method of screening for cardiac defects will depend mainly on the availability of specialist fetal echocardiography. The clinically relevant question at present is to define the patient-specific risk for major cardiac defects based on the measurement of fetal NT, because this will determine the need for specialist fetal echocardiography in the management of the individual patient.

The aim of this study was to define the prevalence of major cardiac defects detectable by specialist fetal echocardiography according to NT thickness at the 11–14-week scan in fetuses with normal karyotype.

ORIGINAL PAPER

METHODS

In our Fetal Medicine Centre fetal echocardiography is routinely performed by specialist pediatric cardiologists in all fetuses presenting with increased NT thickness at the 11 to 13 + 6-week scan and in all patients referred to our unit for a detailed second-trimester scan for assessment of risk for chromosomal defects, in those with a personal or family history of fetal abnormalities and in those with a suspected fetal cardiac or extracardiac defect. Fetal echocardiography is usually carried out transabdominally with probes varying from 7 to 3.5 MHz (Acuson Aspen system, Mountain View, CA, USA). The four-chamber view, outflow tracts, arterial duct, and aortic arch are assessed on cross-sectional imaging and color flow mapping. All ultrasound findings as well as the results of prenatal investigations, such as fetal karyotyping, and data on pregnancy outcome are entered into a fetal medicine database. The latter data are obtained from the maternity units or the patients themselves.

A computer search of the database was carried out to identify all cases undergoing fetal echocardiography between January 1997 and April 2004. The inclusion criteria were measurement of fetal NT thickness and crown–rump length at 11 to 13 + 6 weeks and normal fetal karyotype demonstrated by chorionic villus sampling or amniocentesis, or the live birth of a phenotypically normal baby. We excluded pregnancies in which the scans demonstrated extracardiac fetal abnormalities, those with a previous history of fetal cardiac defects and those with maternal diabetes mellitus.

Cardiac defects are considered to be major if they require surgery or interventional cardiac catheterization within the first year of life. The cardiac defects were grouped into six functional, mutually exclusive categories based on the expected principal hemodynamic consequence of the individual defect or combination of defects: septal defect (ventricular or atrioventricular, common arterial trunk), left inflow obstruction (hypoplastic left heart syndrome, double outlet right ventricle or mitral valve atresia), right inflow obstruction (tricuspid valve atresia), left outflow obstruction (coarctation of the aorta, aortic valve atresia or stenosis), right outflow obstruction (tetralogy of Fallot, pulmonary valve atresia or stenosis), and other (including Ebstein's syndrome, transposition of the great arteries, left isomerism, criss cross and other complex defects). Where more than one of the categories potentially applied, obstruction was given precedence over a septal defect.

The prevalence of major cardiac defects according to fetal NT thickness at the 11 to 13 + 6-week scan was determined. In normal fetuses NT thickness increases with fetal crown–rump length (CRL). The median and 95th centile of NT at a CRL of 45 mm are 1.2 and 2.1 mm, and the respective values at a CRL of 84 mm are 1.9 and 2.7 mm[2]. The 99th centile does not change significantly with CRL and is about 3.5 mm. Fetal NTs were grouped into six categories: below the normal median for CRL, between the median for CRL and less than the 95th centile

for CRL, between the 95th centile for CRL and 3.4 mm, 3.5–4.4 mm, 4.5–5.4 mm and 5.5 mm or more.

RESULTS

Specialist fetal echocardiography was carried in 6921 fetuses with normal karyotype. The median maternal age was 35 (range, 16–50) years and the indications for fetal echocardiography were increased NT thickness (equal to or above the 95th centile for CRL) at the 11 to 13 + 6-week scan ($n = 3444$), detailed second-trimester scan either for assessment of risk of chromosomal defects ($n = 2980$), or previous or family history of fetal abnormalities ($n = 497$). The median gestation at fetal echocardiography was 20 (range, 12–35) weeks; in those having more than one scan the findings in the latest one were considered.

Major cardiac defects were identified in 132 (19.1 per 1000) fetuses (Table 1) and the prevalence increased

Table 1 Types of cardiac defects diagnosed by fetal echocardiography

Type of defect	n
Septal defect	22
AVSD	8
AVSD and left isomerism	5
AVSD and double outlet right ventricle	2
AVSD and hypoplastic right ventricle	1
Common arterial trunk	2
Large VSD	1
VSD and double outlet right ventricle	1
VSD and criss cross	1
AVSD and right isomerism	1
Left outflow obstruction	34
Coarctation of the aorta	20
Coarctation and VSD/AVSD	6
Coarctation and double inlet left ventricle	2
Coarctation and aortic–pulmonary window	1
Aortic stenosis/atresia	5
Right outflow obstruction	25
Tetralogy of Fallot	14
Pulmonary atresia/stenosis	11
Left inflow obstruction	27
HLHS	20
DORV	5
Mitral atresia	1
HLHS and coarctation of the aorta	1
Right inflow obstruction	7
Tricuspid atresia	5
Tricuspid atresia and transposition of the great arteries	1
Tricuspid atresia and aortic atresia	1
Other	17
TGA	9
TGA and right isomerism	1
Double inlet left ventricle and TGA	2
Ebstein's syndrome	1
Left isomerism	1
Criss cross	1
Other complex	2

AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Table 2 Prevalence of major cardiac defects in relation to nuchal translucency (NT) thickness

		Cardiac defect							
NT thickness	n	n	Prevalence per 1000 (95% confidence interval)	Septal defect	Left inflow	Right inflow	Left outflow	Right outflow	Other
< Median	1415	7	4.9 (1.2–8.6)	3	3	0	0	0	1
Median–< 95th centile	2064	18	8.7 (4.7–12.7)	2	2	0	6	6	2
≥ 95th centile–3.4 mm	2365	43	18.2 (12.8–23.6)	7	7	4	9	10	6
3.5–4.4 mm	654	23	35.2 (21.0–49.3)	2	4	1	9	3	4
4.5–5.4 mm	202	13	64.4 (30.5–98.2)	3	3	1	2	3	1
≥ 5.5 mm	221	28	126.7 (82.8–170.5)	5	8	1	8	3	3
Total	6921	132	19.1 (16.0–22.4)	22	27	7	34	25	17
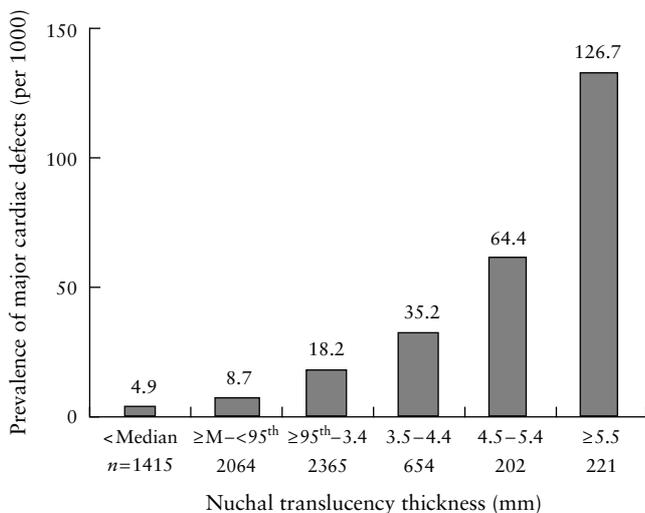
Figure 1 Nuchal translucency thickness distribution in fetuses with normal karyotype and cardiac defects. M, median; 95th, 95th centile.
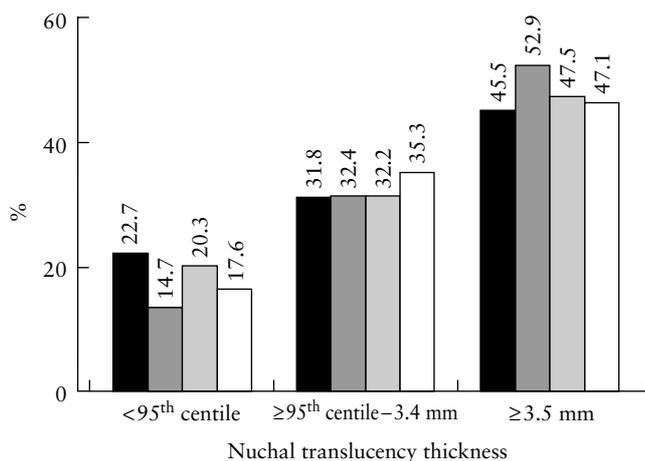
Figure 2 Distribution of different types of cardiac defects with nuchal translucency thickness. ■, septal defect; ▨, outflow obstruction; ▢, inflow obstruction; □, other.

exponentially with fetal NT thickness ($R^2 = 0.99$, $P < 0.0001$; Table 2 and Figure 1). There was no obvious difference in the distribution of NT in the different types of cardiac defects (Figure 2). In 65 (49.2%) of the 132

cases the parents chose to undergo termination of the pregnancy, which was carried out at 13–21 (median 15) weeks. In the remaining 67 cases there were three fetal deaths and 64 livebirths, with three subsequent neonatal deaths.

DISCUSSION

The findings of this study demonstrate that in fetuses with normal karyotype the prevalence of major cardiac defects, detectable by specialist fetal echocardiography, increases exponentially with fetal NT thickness. Furthermore, increased NT is not confined to specific types of cardiac defects.

This study cannot be used to define the screening performance of NT thickness for the detection of cardiac defects because it was not a screening study of an unselected population, but one based on patients referred for specialist fetal echocardiography. In a high proportion of cases the indication for referral was the finding of increased NT at the 11 to 13 + 6-week scan, which was performed routinely as a method of screening for chromosomal defects. We examined more than 1000 fetuses with NT above the 99th centile, making it possible to draw valid conclusions on the prevalence of cardiac defects in such fetuses. Had this been a screening study it would have been necessary to examine more than 100 000 pregnancies to identify a subgroup of fetuses with normal karyotype with substantially increased NT. We believe that the results in fetuses with NT below the 95th centile are also valid because in most of these patients fetal echocardiography was performed routinely as part of our program of screening for chromosomal defects. We excluded patients referred to our unit because of the suspicion of a cardiac or extracardiac fetal abnormality and those at increased risk of fetal cardiac defects either because of a previous history of such defects or because of maternal diabetes mellitus.

Another potential criticism of our study is the method of diagnosing or excluding a major cardiac defect. Ideally the antenatal findings of either absence or presence of a cardiac defect should have been validated by specialist examination of all infants that were liveborn and by postmortem examination in all

cases of pregnancy termination or perinatal death. We selected the pragmatic end-point of a sonographically detectable defect by a pediatric cardiologist specializing in fetal echocardiography.

The prevalence of major cardiac defects in fetuses with NT above the 99th centile (more than 30/1000) is substantially higher than in patients with a family history of cardiac defects and diabetes mellitus (about 20/1000), which are widely accepted as indications for fetal echocardiography. A fetal NT above 3.5 mm is found in about 1% of pregnancies. The risk of major chromosomal abnormalities in such fetuses is very high and increases from about 20% for NT of 4.0 mm to 33% for NT of 5.0 mm and 60% for NT of 5.5 mm or more[2]. Consequently, the first line of management of such pregnancies should be to offer the parents the option of fetal karyotyping by chorionic villus sampling. The prevalence of major fetal defects or fetal death in the chromosomally normal group increases with NT thickness from about 10% for NT of 4.0 mm to 20% for NT of 5.0 mm and 50% for NT of 5.5 mm or more[5,9]. Consequently, in the fetuses with normal karyotype with increased NT, a detailed scan, including fetal echocardiography, should be carried out at 14–16 weeks' gestation to determine the evolution of the NT and to diagnose or exclude many fetal defects.

In fetuses with NT between the 95th and 99th centiles, the prevalence of cardiac defects is about 2%, which is similar to that found in patients with a family history of cardiac defects and diabetes mellitus. The extent to which specialist fetal echocardiography should be offered to these pregnancies, which constitute about 4% of the total population, depends on the availability of such services.

Increased NT is not confined to specific types of cardiac defects, whereas examination of the four-chamber view of the heart in the second trimester is not effective in the identification of fetuses with tetralogy of Fallot, transposition of the great vessels, coarctation of the aorta, and some other lesions. It is therefore possible to combine the two methods of screening (first-trimester NT and second-trimester four-chamber view) to improve the antenatal detection of major cardiac defects.

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